

Early Bactericidal Activity of Moxifloxacin in Treatment of Pulmonary Tuberculosis: a Prospective, Randomized Study

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Moxifloxacin is the most active fluoroquinolone against *Mycobacterium tuberculosis* in vitro. However, data about the efficacy in patients are not available. We enrolled 17 patients with tuberculosis in a prospective, randomized study. After 5 days of monotherapy with either moxifloxacin or isoniazid, we detected significant decreases in mean CFU per milliliter in sputum in both groups. The calculated early bactericidal activities for isoniazid and moxifloxacin were 0.209 and 0.273 log₁₀ CFU per ml of sputum per day, respectively. According to the data from our study, moxifloxacin exhibits an early bactericidal activity that is comparable to that of isoniazid.

Tuberculosis remains one of the deadliest diseases in the world. The World Health Organization (WHO) estimates that more than 8 million new cases of tuberculosis occur each year, and approximately 3 million people die from the disease.

The emerging resistance of *Mycobacterium tuberculosis* to standard antituberculous drugs raises the need for the development of new agents. Fluoroquinolones are of particular interest, because there is no indication of cross-resistance to other antituberculous drugs (9). The clinical efficacy of ciprofloxacin and ofloxacin has already been proven in studies, and despite limited bactericidal activity, these drugs are recommended as second-line therapy by WHO (1). To date, moxifloxacin and gatifloxacin have been shown to be the most active fluoroquinolones against *M. tuberculosis* in vitro (2, 5), and moxifloxacin's antimycobacterial activity has been confirmed in animal studies (12, 14). However, data about the efficacy in patients are not available.

Early bactericidal activity (EBA) of antituberculosis drugs is the rate of decrease in the concentration of tubercle bacilli in sputum during the initial days of therapy and is used to assess the potency of new antituberculous drugs in clinical studies (6).

MATERIALS AND METHODS

We performed a randomized, open, single-center study at the Chest Hospital Heckeshorn, Berlin, Germany, to assess the clinical efficacy of moxifloxacin in patients with pulmonary tuberculosis. The protocol was approved by the Ethical Committee of the Freie Universität, Berlin, and written informed consent was obtained from all subjects prior to enrollment. Seventeen adult, nonimmuno-compromised patients with smear-positive pulmonary tuberculosis and radiological evidence of an infiltrate were orally treated with either 400 mg of moxifloxacin (Bayer, Wuppertal, Germany) once daily ($n = 8$) or 6-mg/kg isoniazid (INH) (Fatol, Schiffswiler, Germany) ($n = 9$) for 5 days. Patients who had received a previous antituberculous chemotherapy within the last 2 years, patients pretreated with any systemic antibacterial agent within 48 h prior to enrollment, and

patients requiring concomitant systemic antibacterial therapy were excluded. The study treatment period was followed by a standard therapeutic regimen for 6 months. Sputum was collected from 4:00 p.m. to 8:00 a.m. before treatment (baseline) and after 2 and 5 days of study treatment. Hematological and biochemical parameters were assessed simultaneously, and electrocardiogram measuring was performed. The count of CFU per milliliter was determined as described previously (11). The EBA was calculated for each patient by the formula $(\log \text{CFU/ml}_{\text{day0}} - \log \text{CFU/ml}_{\text{day5}})/5$ and is given as the mean \pm standard deviation (SD). As recommended by several authors, we defined the EBA as the decrease in log₁₀ CFU per milliliter of sputum per day during the first 5 days of treatment (3, 4).

The numbers of CFU per milliliter before therapy and after 2 and 5 days of study treatment were compared by Wilcoxon's test. The EBAs of moxifloxacin and INH were compared by the Mann-Whitney U test. Statistical analysis was performed with SPSS 11.0 for Windows.

RESULTS AND DISCUSSION

Demographic data of enrolled patients are given in Table 1. Two patients in the moxifloxacin-treated group reported a previous therapy against tuberculosis: One was treated 3 years prior to enrollment with a combination of INH, rifampin, pyrazinamide, and ethambutol. The other patient was treated 12 years prior to study enrollment. Further details about the specific treatment of this patient were not available.

TABLE 1. Patients' characteristics

Characteristic	Result for group	
	INH treated	MOX treated
No. of patients	9	8
No. of patients by sex		
Male	7	5
Female	2	3
Age in yr (mean \pm SD)	54.1 \pm 18.9	50.4 \pm 8.7
Wt in kg (mean \pm SD)	66.0 \pm 12.4	67.7 \pm 7.5
Body mass index (mean \pm SD)	23.7 \pm 4.2	22.7 \pm 3.0
No. with cavitation		
Yes	5	6
No	4	2
No. who reported previous tuberculosis (> 2 yr ago)	0	2

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TABLE 2. Distribution of moxifloxacin MICs in both treatment groups

Group	Moxifloxacin MIC (mg/liter)		
	≤0.125	0.25	0.5
INH treated	2	3	4
Moxifloxacin treated	1	7	0

All patients completed the study. Medication was well tolerated in both groups. No clinically relevant changes in laboratory and ECG parameters (particularly no QT-interval extension) were recorded. Antibiotic susceptibility testing revealed no evidence of resistance to either moxifloxacin or the standard antituberculous drugs (INH, rifampin, ethambutol, pyrazinamide, and streptomycin) in any patient. The INH MIC was ≤0.125 mg/liter in all patients. The distribution of moxifloxacin MICs in both treatment groups is given in Table 2.

The baseline numbers of CFU per milliliter in sputum in the moxifloxacin-treated and INH-treated groups are shown in Table 3. In both groups, a significant decrease in CFU per milliliter in sputum compared to baseline was detected after 5 days of study treatment (Wilcoxon test *P* values for moxifloxacin and INH = 0.028 and 0.015, respectively). Whereas this was to be expected for INH, this is the first evidence for the clinical efficacy of moxifloxacin in patients. In contrast to moxifloxacin, INH treatment led to a faster reduction of the bacterial load already after 2 days of treatment. Nevertheless, the antimycobacterial effect of moxifloxacin seems to be similar to that of INH after 5 days of treatment. The reason for the delayed effect of moxifloxacin compared to that of INH might be due to the different mechanism of action: INH interferes with mycolic acid biosynthesis (13), whereas moxifloxacin mainly affects replicating bacteria by binding to DNA gyrase and topoisomerase IV (8).

The calculated mean EBAs (with 95% confidence intervals [CIs] in parentheses) for INH and moxifloxacin were 0.209 (0.009, 0.394) and 0.273 (0.0001, 0.5462) log₁₀ CFU per ml of sputum per day, respectively. There were no significant differences between the EBAs (*P* = 0.722, Mann-Whitney *U* test).

Despite the limited number of patients, these data suggest that the antimycobacterial activity of moxifloxacin is, with a delay of its onset, similar to that of INH. Different studies determined different EBAs for the same drug and dosage. Therefore, it is important to relate the results of a new drug to a comparator drug (mostly INH) tested in the same study. The EBA of INH (6 mg/kg) has been described in other studies with results of between 1.01 (11 patients) (11) and 0.21 (16 patients) log₁₀ CFU per ml of sputum per day (4). This relative

wide dispersion may be caused by different methodologies—such as, for instance, duration of sputum collection (4)—and by the demographic parameters of the different study populations. Most of the studies that revealed a particularly high EBA for INH were conducted in countries with a high incidence of tuberculosis. The patients enrolled in these studies were mainly younger, had a lighter body weight, and presented a higher pretreatment count of CFU per milliliter than that in patients enrolled in studies in low-incidence countries. This may lead to higher concentrations of the drug in tissue, since the dose of orally administered drugs was not adjusted for body weight (10), and higher pretreatment counts of CFU per milliliter might emphasize the decrease after initial therapy. A multicenter study performed by Sirgel et al. (11) supports the fact that the environment and study population influence the EBA result. In this study, the pretreatment CFU count in the patients in Hong Kong was markedly lower than the pretreatment counts in the patients in the other study centers (Cape Town, South Africa, Nairobi, Kenya, and Madras, India). In consequence, the EBA for INH (at 300 mg) was remarkably lower in the Hong Kong patients (0.37 versus 0.64 to 1.01 log₁₀ CFU per ml of sputum per day) despite an identical methodology.

The EBA for INH in our study (0.209 log₁₀ CFU per ml of sputum per day) corresponds very well with the data from the U.S. study by Hafner et al. mentioned above(4).

However, the EBA of moxifloxacin in our study was even greater than that of the comparator drug, whereas in other studies, INH was revealed to be the most powerful antimycobacterial drug (11). Due to the labor-intensive setting, most studies assessing the EBA, including ours, enroll only a small number of patients, and studies with higher numbers of patients might be needed. Despite this situation, our data demonstrate the already presumed clinical efficacy of moxifloxacin in pulmonary tuberculosis. The calculation of the 95% CI of the difference between the EBA of moxifloxacin and INH (−0.337 to 0.210) revealed that moxifloxacin had at least 61.6% of the antimycobacterial activity of INH in our study. In fact, moxifloxacin is already used as a second-line drug for treatment of tuberculosis in particular cases. Moxifloxacin might be useful for the treatment of multidrug-resistant tuberculosis, because no cross-resistance to other classes of antituberculous drugs is known. Other aspects to consider are the possible side effects of moxifloxacin long-term treatment, which would be required for tuberculosis. Compared to the classic antituberculous drugs, fluoroquinolones can be considered to be better tolerated. However, as yet, there are only limited data to support this issue, and therefore precautions should be taken, particularly when combining fluoroquinolones with other antituberculous drugs (7).

TABLE 3. Change in CFU per milliliter of sputum and EBA in both treatment groups

Treatment	No. of patients	Change in 10 ⁶ CFU/ml			EBA (log ₁₀ CFU/ml of sputum per day)	95% CI of difference
		Baseline	Day 2	Day 5		
INH (6 mg/kg)	9	11.5 ± 8.7	2.6 ± 2.7	1.2 ± 0.1.5	0.209	−0.337–0.210
Moxifloxacin (400 mg)	8	14.2 ± 17.2	4.2 ± 6.0	0.7 ± 0.9	0.273	

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